

nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7, ~~SEQ ID NO: 8, or SEQ ID No: 19~~

REMARKS

Claims 123-165 constitute the pending claims in the present application. Applicants cancel, without prejudice, claim 132. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1-3. Applicants note that the amendments put forth in Paper 28, Paper 33, and Paper 35 have been entered in full. Applicants note with appreciation that the proposed amendments and remarks provided in Paper 32, filed December 17, 2001, will not be entered as they were intended for a related application. Applicants once again apologize for this error, and any inconvenience that may have resulted.

4. In evaluating the Declaration filed December 17, 2001, the Examiner has argued that since the specification discloses that sonic hedgehog is not expressed in adult nervous tissue, one of skill in the art would have to undertake undue experimentation to demonstrate that hedgehog polypeptides function in adult nervous tissues. Applicants disagree with these arguments. Firstly, Applicants point out that the expression, or lack thereof, of hedgehog would not be used by one of skill in the art as an indicator of tissues likely to be responsive to hedgehog signaling. In fact, one might even postulate that tissues expressing hedgehog would be less likely to be responsive to treatment with a hedgehog polypeptide, or that such tissue would require a higher concentration of hedgehog polypeptide in order to overcome the endogenous level of signaling already present in that tissue. One of skill in the art would interpret expression of the hedgehog receptor patched as indicative of a tissue likely to respond to administration of a hedgehog polypeptide. The specification does not explicitly examine vertebrate patched expression, and accordingly does not provide any information to teach away from the enablement of the claimed subject matter. The art, however, supplies ample references which confirm that patched is broadly expressed in many adult tissues, including nervous system tissues (see, for example,

Takabatake et al., 1997; Traiffort et al., 1998; Traiffort et al., 1999; Charytoniuk et al., 2002, enclosed herewith as Exhibits 1-4).

The specification, in light of the state of the art, supports the enablement of the claimed subject matter, and no evidence presented in the specification undermines the enablement of said claimed subject matter. Additionally, however, Applicants point out that to satisfy the requirements under 35 U.S.C. 112, first paragraph, Applicants need not teach why a given method works, but simply must teach one of skill how to practice the claimed method. Therefore, the specification need not present evidence to convince the skilled artisan that the method should work. If one of skill in the art desired additional evidence to confirm that Applicants invention works, then he or she need only perform the routine experimentation of examining the expression of patched in the target tissues. These experiments were subsequently performed by other researchers, and provide confirmatory evidence of **why** Applicants invention works. However, even such routine experimentation is not required to practice the claimed invention. Although understanding the mechanism by which the invention works is interesting and intellectually satisfying, it is not required to practice the claimed methods.

5. Applicants note that the Application is in compliance with the rules regarding sequence disclosures.

6-7. Claims 123-165 are provisionally rejected under the judicially created doctrine of double patenting over claims 11-13 of copending Application No. 08/462386. As previously noted, Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

8-9. Claims 132 and 154 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. To expedite prosecution, Applicants have amended the claims in light of the Examiner's suggestions. Such amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are respectfully requested.

a. Applicants have amended claim 154 to more particularly point out the claimed subject matter. Applicants amendments to claim 154 are believed to obviate the rejection.

b. Claim 132 is rejected because the recitation of "the effect of a naturally-occurring hedgehog protein" allegedly cannot be unambiguously understood by one of skill in the art. Applicants contend that the specification provides an extensive discussion of the effects of hedgehog signaling in tissues derived from all three germ layers. Additionally the art is replete with references disclosing examples of the functions of hedgehog signaling. Accordingly, Applicants maintain that one of skill in the art would readily be able to recognize whether the effect of the claimed methods is consistent with an effect of a naturally occurring hedgehog protein. Applicants do not argue that hedgehog signaling has many roles in diverse tissues, however, that does not prevent one of skill in the art from recognizing an effect which mimics an effect of a naturally occurring hedgehog protein. The effects of hedgehog signaling can be readily recognized by one of skill in the art when they are observed.

Nevertheless, to expedite prosecution, Applicants have cancelled claim 132. Cancellation of claim 132 is not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

10-11. Claims 123-165 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to enable one of skill in the art to practice the claimed invention. To expedite prosecution, Applicants have amended the claims to more particularly point out the hedgehog polypeptides for use in the claimed methods. Such amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

The rejection under 35 U.S.C. 112 appears to have several components. Applicants will attempt to specifically address each of these bases for the rejection. Firstly, the Office Action alleges that the specification teaches away from methods of using hedgehog polypeptides in adult tissues. Applicants have addressed this point in great detail in Section 4 above. Briefly, Applicants maintain that one of skill in the art would not be dissuaded from practicing Applicants' invention merely because of preliminary evidence demonstrating that Sonic hedgehog is not expressed in adult tissues. One of skill in the art would be influenced by the expression of the hedgehog receptor patched as indicative of responsiveness of a tissue to

hedgehog signaling. Accordingly, Applicants maintain that the specification provides no evidence that would teach away from the claimed methods.

Applicants further note that the test for enablement is not whether one of skill in the art believes that the invention will work as Applicants have described. A patent application is neither a peer reviewed publication nor a grant proposal, and Applicants need not seek the approval of any or all of the research community in order to have an operable and enabled invention. Rather the standard for enablement is whether one of skill in the art can practice the invention in light of Applicants' disclosure. Applicants submit that one of skill in the art could practice the claimed invention following the teachings of the disclosure even if she did not believe that Applicants' invention would work. Accordingly, Applicants contend that the claims are enabled throughout their scope, and that post-filing evidence further supporting the claimed subject matter does not demonstrate that undue experimentation is required to practice the claimed methods. Rather, such post-filing evidence merely confirms the teachings of the disclosure.

The rejection additionally appears to concern the degree of variation from the recited polypeptides reasonably entitled to fall within the scope of the claims. To expedite prosecution, Applicants have amended the claims to more particularly point out the claimed polypeptides and fragments. Applicants additionally point out that the polypeptides recited in the claimed methods are described by both sequence and by a functional limitation (the ability to bind patched). Such a functional limitation allows one of skill in the art to readily recognize the polypeptides for use in the claimed methods, and further allows one of skill in the art to evaluate whether a variant is operable for use in the present invention. Applicants note that in accordance with MPEP 2164.08(b), “[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art.” This standard has been upheld in the courts, and permits a claim to encompass a finite number of inoperable embodiments so long as inoperable embodiments can be determined using methodology specified in the application. See, for instance, *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976).

Given that one of skill in the art can readily evaluate whether a polypeptide variant is useful in the methods of the claimed invention, and given that both the MPEP and the courts acknowledge that inoperative embodiments may exist within the scope of a claim, the only remaining question is whether the making and testing of polypeptide variants constitutes undue experimentation. Applicants contend that such experimentation is routinely practiced in the art and is not undue. "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988).

Applicants provided considerable information to one of skill in the art regarding the construction of polypeptide variants. Additionally, the art at the time of filing no longer relied upon purely rational choices of conserved amino acid substitutions to construct polypeptide variants. The fields of combinatorial and scanning mutagenesis had trivialized the once complex and painstaking process of making and testing polypeptide variants long before the filing of the present application (for examples see Reidhaar-Olson and Sauer, 1988; Wissmann et al., 1991; Delagrange et al., 1993; enclosed herewith as Exhibits 5-7). These techniques were routinely practiced, and allow a wide range of amino acid substitutions to be made and tested for the maintenance or disruption of functional properties without undue experimentation. MPEP 2164.05(a) makes clear that the "specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*". Such is the case here. Techniques for synthesizing, testing and identifying sequences which would possess the recited structures and functions were well known in the art at the time of filing and routinely carried out. Accordingly, one of skill in the art faced with the task of constructing and identifying polypeptides which meet the functional limitations of the pending claims would not expect to expend any more effort than normally required.

Applicants contend that the claims are enabled throughout their scope. Applicants' disclosure provides methods for using hedgehog polypeptides in adult neural tissue, and the prevailing subsequent evidence in the field supports Applicants invention. The test of

enablement is not whether, at the time of filing of the Application, one of skill in the art believed that Applicants invention would work. The test for enablement is not whether one of skill in the art understood the mechanism by which the invention works. The test for enablement is whether the disclosure describes how to make and use the invention. Reconsideration and withdrawal are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

Respectfully Submitted,

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